IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Munishkin, A and A. Grossman	
Application No.:	09/844,935	
		Art Unit: 1634
Filed:	April 27, 2001	Examiner: Chakrabarti
Title:	Compositions, Methods, Kits, and Apparatus for Determining the Presence or Absence of Target Molecules	
Docket No.:	1009-05	

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Sir:

In Reply to the Office Action mailed September 5, 2002, Applicants file the following response.

Remarks

Claims 1-13 are pending in this application. Applicants cancelled claim 10 in Preliminary Amendment dated April 27, 2001.

Restriction Requirement

Examiner contends that claims 1-8, 11 and 12 (Group I) and claim 9 (Group II) are distinct inventions. Examiner also contends that claims 1-8, 11, and 12 (Group I) and claim 13 (Group III) are distinct inventions. Further, Examiner contends that the inventions of Group II and Group III are unrelated thereby requiring a restriction of claims. Applicants respectfully traverse this restriction requirement.

The Examiner must provide reasons and/or examples to support conclusions which require restriction of claims. M.P.E.P 803. It is the opinion of Applicants that the Examiner failed to attain this threshold.

Claims for the product (Group I) are not distinct from the process of making the product (Group III). Examiner correctly states the test for distinctness between a process of making and a product made as:

> The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make a materially different product or (2) that the product as claimed can be made by another and materially different process (M.P.E.P. 806.05(f)). *Office Action* dated 9/5/2002, page 2-3.

The Examiner opines that "the product can be made chemically or by hand." *Office Action* dated Sept.5, 2002, page 3. Examiner's statement does not meet the requirements of M.P.E.P. 806.05(f) because it does not show the process as claimed can be used to make a materially different product or show that the product as claimed can be made by another and materially different process.

Applicant's process of making a product (claim 13), in general, describes a method of making an RNA molecule which can bind to a target molecule and be acted upon by an RNA replicase to create a second RNA molecule. Examiner does not provide any example which describes a method of making the product as claimed by a process materially different than Claim 13. Claim 13 not only describes the making of a specific RNA sequence, but also the selection of a sequence which binds to a specific target molecule. A product which "can be made chemically or by hand" can make a specific RNA sequence, but it cannot necessarily make a sequence which is selected to bind the target molecule. Thus, Examiner has failed to provide sufficient reasons why the claims of Group I and Group III should be restricted as required by M.P.E.P 803.

Examiner has failed to meet the threshold necessary to require a restriction requirement between Group I and Group III. Thus, Applicants respectfully request Examiner withdraw the restriction requirement and reconsider Claim 13 for further examination.

Since the claims of Group I and Group III are not distinct, the claim of Group II (Claim 9) may be joined with the claims of Groups I and III. The claim of Group II is related to the other claims because it is a process of use. Where claims to all three categories, product, process of making, and process of use, are included in a national application, a three way requirement for restriction can only be made where the process of making is distinct from the product. If the process of making and the product are not distinct, the process of using may be joined with the claims directed to the product and the process of making the product even though a showing of distinctness between the product and the process of using the product can be made. 37 CFR 1.141, M.P.E.P. 806.05(i).

Thus, Applicants request the withdrawal of the restriction requirement and request Examiner to examine claims 1-9 and 11-13 in this application. Although Applicants traverse Examiner's restriction requirement, Applicants elect claims 1-8, 11, and 12 (Group I) as required by MPEP 818 for further prosecution.

Rejection of Claims 1-5, and 7

Claims 1-5, and 7 are rejected under 35 USC 102(b) as being anticipated by Marsh, et al. (Nucleic Acids Research, (1998), 16, (3), 981-995). Applicants respectfully disagree.

Examiner states that Marsh discloses:

> [A] method of determining the presence or absence of a target molecule comprising the steps of: (a) providing a first RNA molecule which can bind to a target molecule... (b) imposing binding conditions on a sample potentially containing target molecules in the presence of first RNA molecule, in the presence of the target molecule, first RNA molecules forms a target-first RNA molecule complex to form a first modified sample, (c) imposing RNA replicase reaction conditions on the first modified sample... to form a second RNA molecule in the presence of target to make a second modified sample, and (d) monitoring second modified sample for the presence of the second RNA molecule or its complement, which presence or absence is indicative of the presence or absence of the target molecule. *Office Action* dated 9/5/02, pp. 4-5.

Examiner also states that Marsh discloses "that section C may serve as a non base-paired spacer to facilitate access of the replicase to the promoter."

Section 102 of Title 35 provides the novelty requirement for patentability. In order for a prior art reference to anticipate a claim it must teach each and every element of that claim. See also, M.P.E.P. § 2131. The Court of Appeals for the Federal Circuit states: "the identical invention must be shown in as complete detail as is contained in the... claim." Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236 (Fed.Cir. 1989).

Applicants claim (see Claim 1) a composition for determining the presence or absence of a target molecule comprising a first RNA molecule which binds a target molecule and has the formula:

5'-A-B-C-D-E-3';

wherein sections A and E are replicated by a replicase, sections Band D bind the target molecule, and section C is capable of preventing replication of the first molecule by the RNA replicase. In this composition, the binding of B and D to the target molecule allows the replicase to form a second RNA molecule with the formula:

5'-E'-X-A'-3'

Marsh cannot anticipate Applicants' claimed invention because it does not teach each and every element of Claim 1. First, Marsh is very specific in characterizing the internal promoter region of BMV RNA3. (Marsh, abstract, page 981). Marsh teaches the transcription of an RNA molecule from a DNA molecule, the addition of a replicase to this RNA molecule, and the replication of the RNA molecule creating a double stranded replicase product. (Marsh, materials and methods, page 983).

Importantly, (i) Marsh does not teach the replication of an RNA molecule while the RNA molecule is bound to the target molecule. Contrary to Marsh, Applicants' claim the replication of the RNA molecule while sections B and D are bound to the target molecule; (ii) further, Marsh teaches replication creating a double stranded replicase product, whereas Applicants' claim the replication of a second RNA molecule with a different sequence than the first RNA molecule because the second RNA molecule would not include section C or parts of section B and D. Because Marsh teaches a double stranded replicase product, the replicated strand is inherently equal to the initial strand, and is *not* a different sequence (contrast this with Claim 1 of the present invention).

Unlike the presently claimed invention, Marsh never discloses any section C which can be used to prevent or control replication of RNA molecule. The Examiner even states that "Marsh does not teach section C of the RNA molecule which section is capable of preventing replication of the first molecule by the RNA replicase." *Office Action* dated 9/5/2002, page 7. Marsh used a BMV promoter which contained a poly A tract, but this tract was never used to prevent replication. This poly A tract occurred naturally within the promoter (and was not engineered to be added as in Claim 1 of Applicants' claimed invention) and was thought of only as a spacer and not as a controller of replication. Marsh's disclosure simply teaches the replication and analysis of the RNA promoter, and it does not teach any method to determine the presence or absence of a target molecule.

Clearly, Marsh fails the anticipation test as required by 35 USC 102 and the Federal Circuit. From the above discussion, it is evident that Claim 1 of the instant application is not anticipated by Marsh and is thus allowable. Furthermore, Claims 2-6 and 7 depend form Claim 1 in the instant application. It is axiomatic in patent law that if an independent claim is allowable, such as in the present case with Claim 1, then those claims which depend therefrom are also allowable given that the dependent claims incorporate all of the limitations recited in the independent claim. See *In re* Fine, 837 F.2d 1071, 1076, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988). Given the allowable subject matter of Claim 1, as argued above, dependent Claims 2-5 and 7, which only add additional limitations, define

allowable subject matter. Hartness International, Inc. v. Simplimatic Engineering Co., supports this proposition, which held "[a] *fortiori*, [the] dependent claim... was nonobvious (and novel) because it contained all of the limitations of [the independent] claim...plus a further limitation." 819 F.2d 1100, 1108, 2 USPQ2d 1826, 1831 (Fed. Cir. 1987).

Therefore, Applicants respectfully request withdrawal of the rejection of Claims 1-5 and 7 and be reconsidered by the Examiner.

Rejection of Claims 6 and 8

Claims 6 and 8 are rejected under 35 USC 103(a) as being unpatentable over Marsh, et al. (Nucleic Acids Research, (1988), 16 (3) 981-995) in view of Spiegelman (U.S. Patent 3,444,043, issued May 13, 1969). Applicants respectfully disagree.

Examiner states that Marsh discloses: (as described above)

> [A] method of determining the presence or absence of a target molecule comprising the steps of: (a) providing a first RNA molecule which can bind to a target molecule... (b) imposing binding conditions on a sample potentially containing target molecules in the presence of first RNA molecule, in the presence of the target molecule, first RNA molecules forms a target-first RNA molecule complex to form a first modified sample, (c) imposing RNA replicase reaction conditions on the first modified sample... to form a second RNA molecule in the presence of target to make a second modified sample, and (d) monitoring second modified sample for the presence of the second RNA molecule or its complement, which presence or absence is indicative of the presence or absence of the target molecule. *Office Action* dated 9/5/2002, pages 4-6.

Examiner acknowledges that Marsh does not teach a composition by providing paired RNA molecules *and* does not teach a section C which is capable of preventing replication of the first molecule by the replicase.

Examiner states that Spiegelman teaches the customized preparation of RNA templates and teaches section C of the RNA molecule which is capable of preventing replication of the first molecule by RNA replicase.

In order to establish a *prima facie* case of obviousness, "there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references) must teach or suggest all of the claim limitations." M.P.E.P. § 2143, see also *In re* Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir.1991).

A *prima facie* case of obviousness is not established in the instant case because Marsh in view of Spiegelman does not teach nor suggest that which is claimed by

Applicants in the present invention. As described above, Marsh characterizes the internal promoter region of BMV RNA3. Marsh teaches the transcription of an RNA molecule from a DNA molecule, the addition of a replicase to this RNA molecule, and the replication of the RNA molecule creating a double stranded replicase product. Marsh does not teach the replication of the RNA molecule while the RNA molecule is bound to the target molecule, the replication of an RNA molecule with a different sequence than the first RNA molecule, nor the use of a section C which can be used to prevent replication of the first molecule (as described above).

Further, Spiegelman fails to rectify the deficiencies in Marsh to establish a *prima facie* case of obviousness. Spiegelman teaches the formation of compounds which interfere with the recognition mechanism between RNA and RNA replicase. Examiner notes that Spiegelman teaches the customized preparation of RNA templates which could be used to produce mutants. Spiegelman simply suggests a method of making mutations in RNA which could be used to analyze the binding characteristics of the replicase to the RNA (Column 5, lines 1-8 of US 3,444,043). Applicants' claimed invention is not a mutation which can just be used to analyze replicase binding mechanisms. Applicants' claimed invention binds to a target molecule at the same time as it is being replicated by a replicase.

Examiner also notes that Spiegelman teaches a section C which is capable of preventing the replication of the first molecule by the RNA replicase. (*Office Action* dated 9/5/02, page 7). Spiegelman neither teaches nor suggests the engineering of a section C into an RNA molecule such that replicase binding and replication can only occur while the RNA molecule is bound to its target molecule. Instead, Spiegelman suggests the use of a section "C" to inhibit replicase activity completely, rather than selectively preventing replicase activity as described in Applicants' claimed invention. (US 3,444,043 column 8, lines 45-50).

Examiner notes that Spiegelman states;

> There is good evidence that the replicase recognizes the particular sequence of nucleotides at the beginning and end of the biologically active viral RNA template...it is inferred from this recognition pattern that the intermediate portion of the template is not essential...it is thought that the RNA forms a circle and these two recognition sequences of the molecules overlap each other to provide double stranded regions: such overlapping regions could afford, therefore, identification of the RNA molecule in a single, rapid screening process. *Office Action* dated 9/5/2002, page 8.

Spiegelman does not teach nor suggest any specific type of "single, rapid screening process." Spiegelman simply suggests use of the overlapping RNA regions as part of a screening process. (Spiegelman, column 4, lines 57-75). Further, Spiegelman does not indicate what the screening process would be used to find. The Federal Circuit has indicated that a prior art reference that gives only general guidance and is not at all specific as to particular forms of a claimed invention and how to achieve it, may make a certain approach obvious to try, but does *not* make the invention obvious. Ex Parte Obukowicz, 27

USPQ2d 1063, citing In re O'Farrell, 853 F.2d 894, 7 USPQ2d 1673, 1682 (Fed. Cir. 1988). This suggestion is very broad and provides no evidence to combine with Marsh to suggest Applicants' claimed invention is obvious.

Thus, one of ordinary skill in the art would not have been able to combine Marsh in view of Spiegelman in order to arrive at the invention claimed by Applicants. Therefore, Applicants respectfully request that the present rejection be reconsidered and withdrawn.

Rejection of Claim 11

Claim 11 is rejected under 35 USC 103(a) as being unpatentable over Marsh, et al. (Nucleic Acids Research, (1988), 16 (3) 981-995) in view of the Stratagene Catalog (1988, page 39). Applicants respectfully disagree.

As described above, Marsh characterizes the internal promoter region of BMV RNA3. Marsh teaches the transcription of an RNA molecule from a DNA molecule, the addition of a replicase to this RNA molecule, and the replication of the RNA molecule creating a double stranded replicase product. Unlike what is claimed by Applicants, Marsh does not teach nor suggest the replication of the RNA molecule while the RNA molecule is bound to the target molecule, the replication of an RNA molecule with a different sequence than the first RNA molecule, nor the use of a section C which can be used to prevent replication of the first molecule (as described above).

The Stratagene catalog does not remedy the deficiencies in Marsh to render Claim 11 obvious. Examiner states that the Stratagene catalog teaches a motivation to combine reagents into kit format. The Stratagene catalog does not teach nor suggest the replication of an RNA molecule while the RNA molecule is bound to the target molecule, the replication of an RNA molecule with a different sequence than the first RNA molecule, nor the use of a section C which can be used to prevent replication of the first molecule.

Individually or combined, Marsh in view of the Stratagene catalog does *not* establish a *prima facie* case of obviousness as outlined by the Federal Circuit (see above). Therefore, Applicants respectfully request that the rejection of Claim 11 be reconsidered and withdrawn.

Rejection of Claim 12

Claim 12 is rejected under 35 USC 103(a) as being unpatentable over Marsh, et al. (Nucleic Acids Research, (1988), 16 (3) 981-995)) in view of Spiegelman (U.S. Patent 3,444,043 issued May 13, 1969) further in view of the Stratagene Catalog (1988, page 39). Applicant respectfully disagrees.

As described above, Marsh characterizes the internal promoter region of BMV RNA3. Marsh teaches the transcription of an RNA molecule from a DNA molecule, the

addition of a replicase to this RNA molecule, and the replication of the RNA molecule creating a double stranded replicase product. Unlike Applicants' claim, Marsh does not teach nor suggest the replication of the RNA molecule while the RNA molecule is bound to the target molecule, the replication of an RNA molecule with a different sequence than the first RNA molecule, nor the use of a section C which can be used to prevent replication of the first molecule (as described above).

Spiegelman fails to rectify the deficiencies of Marsh in order to establish a *prima facie* case of obviousness. Spiegelman teaches the formation of compounds which interfere with the recognition mechanism between RNA and RNA replicase. Examiner notes that Spiegelman teaches the customized preparation of RNA templates which could be used to produce mutants. Spiegelman simply suggests a method of making mutations in RNA which could be used to analyze the binding characteristics of the replicase to the RNA (Column 5, lines 1-8 of US 3,444,043). Applicants' claimed invention binds to a target molecule at the same time as it is being replicated by a replicase.

Examiner notes that Spiegelman states;

> There is good evidence that the replicase recognizes the particular sequence of nucleotides at the beginning and end of the biologically active viral RNA template...it is inferred from this recognition pattern that the intermediate portion of the template is not essential...it is thought that the RNA forms a circle and these two recognition sequences of the molecules overlap each other to provide double stranded regions: such overlapping regions could afford, therefore, identification of the RNA molecule in a single, rapid screening process.

Spiegelman does not teach nor suggest any specific type of "single, rapid screening process." Spiegelman simply suggests use of the overlapping RNA regions as part of a screening process. (Spiegelman, column 4, lines 57-75). Further, Spiegelman does not indicate what the screening process would be used to find. The Federal Circuit has indicated that a prior art reference that gives only general guidance and is not at all specific as to particular forms of a claimed invention and how to achieve it, may make a certain approach obvious to try, but does not make the invention obvious. Ex Parte Obukowicz, 27 USPQ2d 1063, citing In re O'Farrell, 853 F.2d 894, 7 USPQ2d 1673, 1682 (Fed. Cir. 1988).

The Stratagene catalog does not remedy the deficiencies of Marsh and Spiegelman in order to make Claim 12 obvious. Examiner states that the Stratagene catalog teaches a motivation to combine reagents into kit format. The Stratagene catalog does not teach, as is claimed by Applicants, the replication of an RNA molecule while the RNA molecule is bound to the target molecule, the replication of an RNA molecule with a different sequence than the first RNA molecule, nor the use of a section C which can be used to prevent replication of the first molecule.

Individually or combined, Marsh in view of Spiegelman and further in view of the Stratagene catalog does not establish a *prima facie* case of obviousness. Therefore,

Applicants respectfully request that the rejection of Claim 12 be reconsidered and withdrawn.

Conclusion

In view of the foregoing, all pending claims are deemed to define allowable subject matter. Accordingly, Applicants respectfully request reconsideration and withdrawal of all rejections and restrictions and that a Notice of Allowance be issued. The Examiner is invited to telephone the undersigned attorney for the Applicants at (603) 890-4099 in the event that such communication is deemed to expedite prosecution of this application.

Respectfully submitted,

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Date: December 3, 2002